Proposed Decision Memo for Autologous Blood Derived Products for Chronic Non-Healing Wounds (CAG-00190R2)

Decision Summary

The Centers for Medicare and Medicaid Services (CMS) proposes the following:

The evidence is not adequate to determine that autologous platelet rich plasma (PRP) is reasonable and necessary for the treatment of chronic non-healing cutaneous wounds, acute surgical wounds when the autologous PRP is applied directly to the closed incision, or dehiscent wounds. CMS is proposing to issue non-coverage determinations for acute surgical wounds when the autologous PRP is applied directly to the closed incision and for dehiscent wounds.

In addition, we propose to make no change to the NCD addressing Blood-Derived Products for Chronic Non-Healing Wounds (Pub. 100-3, 270.3.D). In accordance with section 310.1 of the National Coverage Determinations Manual, Medicare covers the routine costs in Federally sponsored or approved clinical trials assessing the efficacy of autologous PRP in treating chronic, non-healing cutaneous wounds.

We are requesting public comments on this proposed determination pursuant to Section 1862(l) of the Social Security Act. We are particularly interested in comments that include new evidence we have not reviewed here. After considering the public comments and any additional evidence, we will make a final determination and issue a final decision memorandum.

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Proposed Decision Memo

TO: Administrative File: CAG-00190R2
Autologous Blood-Derived Products for Chronic Non-Healing Wounds (Second Reconsideration)

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SUBJECT: Proposed Coverage Decision Memorandum for Autologous Blood-Derived Products for Chronic Non-Healing Wounds

DATE: December 20, 2007

I. Proposed Decision

The Centers for Medicare and Medicaid Services (CMS) proposes the following:

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II. Background

Summary of the Disease

A cutaneous wound is a disruption of the normal anatomic structure and function of the skin. A wound is described as partial thickness where the disruption involves the outer two layers of the skin (the epidermis and the dermis) or as full thickness where the disruption involves all three layers (i.e., the epidermis, dermis and subcutaneous tissue).

Wound healing is a dynamic, interactive process that involves multiple cells and proteins. There are three progressive stages of normal wound healing: inflammatory, tissue formation, and tissue remodeling (Singer, 1999). During the inflammatory stage, platelets and neutrophils migrate to the area to stabilize the wound and begin the process of healing. Each cell releases various proteins generally referred to as growth factors to accomplish these tasks. During the tissue formation stage, two other cells, the macrophage and the fibroblast, gather in the wound area to continue the process of healing by stimulating the early phase of wound remodeling and strengthening. New tissue, called granulation tissue, is created in the wound. New blood vessels are created to nourish the granulation tissue. Skin cells begin preparations to eventually cover the wound. The tissue remodeling stage continues the remodeling and strengthening processes and leads to complete closure of the wound. The typical normal wound healing duration is about four weeks.

There are two general types of wounds: acute and chronic. A wound is labeled “acute” when it has yet to proceed through the three stages of normal wound healing. The presumption is that an acute wound will be repaired in an orderly and timely process (Robson, 2006). By contrast, a chronic wound is of sufficient age that it should have progressed through the three stages, but failed to do so. Hence, a wound is labeled “chronic” when it has failed to repair itself. In the 2003 decision memorandum (CAG-00190N) a chronic wound was considered to be one that has failed to heal within thirty days; CMS is applying this same consideration to this proposed decision memorandum (PDM).

A dehiscent wound is typically an incisional site that was closed at the end of surgery that has subsequently split open along the suture lines. Wound dehiscence is a potential complication that occurs as a result of poor wound healing.

Because normal wound healing involves many variables that interact in a dynamic and interactive manner, the reasons for abnormal wound healing are usually multi-factorial. Multiple physiologic and biochemical defects can lead to a failure to heal (Singer, 1999). The presence of co-morbid medical conditions increases this variability. For example, patients with diabetes suffer from vascular disease, which can limit the ability of wound healing-relevant cells and their growth factors to reach the wound area. Adding to the variability is the potential for each co-morbid condition to impact the normal wound healing process in a different manner. For example, the factors underlying the cause of a diabetic ulcer can, and usually are, different from the factors behind a pressure ulcer.

Given the multi-factorial manner of wound development, healing and failure to heal, with resultant different wound types, the management of chronic, cutaneous wounds is increasingly tailored to the specific type of wound. There are some treatments and strategies that are commonly used regardless of wound type such as debridement of dead tissue in the wound, maintaining a moist wound environment, infection control, and the reduction of recurring trauma to the wound. However, other procedures are customized by wound type; for example, intense regulation of the hemoglobin A1C level in a patient with a diabetic foot ulcer, or the restoration of arterial perfusion in a patient with an ulcer due to arterial insufficiency.

Background of the Procedure

Platelet releasates, including multiple growth factors, have been used for the treatment of wounds since the mid 1980s (Driver, 2006). An example is becaplermin, which is an FDA-approved product that contains a single growth factor called platelet-derived growth factor (PDGF). Alternatively, autologous PRP provides a concentrated source of platelets and the numerous types of growth factors contained in their granules. Most notable are PDGF and transforming growth factor-ß (i.e., TGF-ß1 and TGF- ß2) but also include insulin-like growth factor, vascular endothelial growth factor, as well as other growth factors (Steigmann, 2005).

Platelet-rich plasma is produced in an autologous or homologous manner. Autologous PRP is comprised of blood from the patient who will ultimately receive the PRP. Alternatively, homologous PRP is derived from blood from multiple donors.

Platelet-rich plasma is prepared by extracting a small amount of a person's blood and sequestering and concentrating the platelets using a centrifuge. The platelet's alpha granules are then stimulated to release their growth factors by the addition of thrombin (called the platelet activation method) or the growth factors are released by physically disrupting (or lysating) the alpha granules (called the freeze-thaw method) (Steigmann, 2005).

III. History of Medicare Coverage

In 1992, CMS issued a national non-coverage determination for autologous, platelet-derived wound healing formulas intended to treat patients with chronic, non-healing wounds.

In December 2003, CMS issued a national non-coverage determination for use of autologous PRP for the treatment of chronic non-healing cutaneous wounds except for routine costs when used in accordance with the clinical trial policy defined in section 310.1 of the National Coverage Determinations Manual.

In April 2005, CMS issued a national coverage determination (NCD) to correct the erroneous potential for local coverage of becaplermin, printed in the 270.3 section of the NCD manual, entitled "Blood-Derived Products for Chronic Non-Healing Wound." CMS deleted the erroneous sentences and inserted the correct statement that "Coverage for treatments utilizing becaplermin, a non-autologous growth factor for chronic non-healing subcutaneous wounds, will remain nationally non-covered under Part B based on §1861(s)(2)(A) and (B) because this product is usually administered by the patient."

Current Request

On June 20, 2007, Cytomedix submitted a formal request to CMS to reconsider coverage of autologous blood-derived products when used for the treatment of chronic non-healing wounds.

Autologous PRP is a prevalent blood product used for treating chronic non-healing wounds, open cutaneous wounds, soft tissue, and bone.

Cytomedix submitted new evidence and requested CMS to re-evaluate the coverage of autologous PRP gel for the following open-cutaneous wounds, including chronic wounds:

1. Wounds caused by an acute surgical incision or dehiscence.

2. Full-thickness chronic wounds that have failed an adequate course of standard wound therapy.

Benefit Category

For an item or service to be covered by the Medicare program, among other things, it must meet one of the statutorily defined benefit categories outlined in the Social Security Act.

There is no specific Medicare benefit category for autologous blood-derived products for treatment of chronic non-healing wounds. However, these services, at a minimum, fall within the benefit categories of physician's service (§1861(s)(1) of the Act) and "incident to" a physician's service (§1861(s)(2)(A) of the Act).

This may not be an exhaustive list of all applicable Medicare benefit categories for this item or service.

IV. Timeline of Recent Activities

June 25, 2007	CMS formally opened a national coverage analysis on Autologous Blood-Derived Products for Chronic Non-Healing Wounds.
	The initial public comment period opened.

July 25, 2007	The initial public comment period closed.
September 18, 2007	Cytomedix and wound care experts meeting at CMS.
October 15, 2007	Organogenesis meeting at CMS.

V. FDA Status

The AutoloGel™ System has been cleared by the FDA under Section 510(k) in a determination that the device is substantially equivalent (for the following listed indications) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976. The device "is intended to be used at point-of-care for the safe and rapid preparation of platelet-rich plasma (PRP) gel from a small sample of a patient's own blood. Under the supervision of a healthcare professional, the PRP gel produced by the AutoloGel™ System is suitable for exuding wounds, such as leg ulcers, pressure ulcers and for the management of mechanically or surgically-debrided wounds."

FDA concluded, "Based on the clinical performance information, it can be concluded that AutoloGel is substantially equivalent to the marketed wound dressing IPM Wound Gel." (FDA 510(k) summary accessed at http://www.fda.gov/cber/510ksumm/k060007S.pdf accessed November 15, 2007.)

VI. General Methodological Principles

When making national coverage determinations, CMS evaluates relevant clinical evidence to determine whether or not the evidence is of sufficient quality to support a finding that an item or service falling within a benefit category is reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member. The critical appraisal of the evidence enables us to determine to what degree we are confident that: 1) the specific assessment questions can be answered conclusively; and 2) the intervention will improve health outcomes for patients. An improved health outcome is one of several considerations in determining whether an item or service is reasonable and necessary.

Methodological principles of study design that are used to assess the literature on a therapeutic or diagnostic item or service for specific conditions can be found in Appendix A. In general, features of clinical studies that improve quality and decrease bias include the selection of a clinically relevant cohort, the consistent use of a single good reference standard, and the blinding of readers of the index test, and reference test results.

Public comment sometimes cites the published clinical evidence and gives CMS useful information. Public comments that give information on unpublished evidence such as the results of individual practitioners or patients are less rigorous and therefore less useful for making a coverage determination. CMS uses the initial public comments to inform its proposed decision. CMS responds in detail to the public comments on a proposed decision when issuing the final decision memorandum.

VII. Evidence

A. Introduction:

This PDM focuses on the use of PRP in chronic, non-healing wounds; dehiscent wounds; or in acute wounds when PRP is applied directly upon the closed incision site (i.e., a cutaneous application). Consequently, the various subcutaneous uses of PRP (for example, during sinus or dental surgery, or for the treatment of chronic elbow tendinosis) are not addressed in this document. In addition, only autologous PRP is addressed and not PRP obtained from homologous sources.

A high quality of evidence is critical to determine whether an intervention improves the patient's health outcome. The highest quality of clinical evidence generally comes from prospective, controlled clinical trials. Hence, in this PDM, CMS gives preference to results from controlled clinical trials that investigated autologous PRP. However, we also review other published evidence from observation studies as well as the professional opinions found in position statements or in review articles. We also consider public comments and evidence submitted for our review.

For chronic, non-healing wounds and for dehiscent wounds, CMS continues to use the primary outcome of interest that was used in the original NCD (CAG-00190N)–incidence of complete wound healing (also known as complete wound closure or one hundred percent re-epithelialization). A definitive outcome such as this allows for a confident generalization of the available evidence across studies, different types of studies, different types of wounds, and to the Medicare population. This is an important consideration given the variability of wound pathophysiology, the propensity for the use of an uncontrolled design in wound studies and since many patients in studies are less than 65 years of age.

Time to complete wound healing and incidence of wound infection are two additional outcomes that have been reported in the clinical literature. However, the incidence of complete wound closure is the most commonly used primary outcome.

For acute, surgical wounds that were closed upon completion of the surgical procedure, potential outcomes are incidence of dehiscence, severity of incisional pain and incidence of infection.

In June, 2006 the Food and Drug Administration (FDA) issued a guidance document regarding the clinical investigation of chronic cutaneous ulcer and burn wounds titled "Guidance for Industry. Chronic Cutaneous Ulcer and Burn Wounds—Developing Products for Treatment." The salient points from this document include:

- The guidance specifically addresses only three types of chronic cutaneous ulcers: venous stasis ulcers, diabetic foot ulcers, and pressure ulcers (FDA guidance, page 1).
- FDA defines a chronic cutaneous ulcer as "a wound that has failed to proceed through an orderly and timely series of events to produce a durable structural, functional, and cosmetic closure" (FDA guidance, page 1). CMS considers this to be an important distinction from an acute wound, which has not had the opportunity to proceed through this orderly and timely series of events.
- Regarding clinical trial design, randomization is "particularly important for reducing bias in wound indication trials because standard wound care procedures and baseline wound characteristics generally have a profound effect on outcome" (FDA guidance, page 5). FDA notes that standard care refers to generally accepted wound care procedures, which can vary from institution to institution and hence confound the assessment of the outcome (FDA guidance, page 8). To emphasize the importance of this point, the guidance devotes over three pages to the subject of standard care considerations (FDA guidance, pages 8-12). Of note, the guidance suggests the use of a "standard-of-care" or run-in phase, which is an initial stage of the trial where only standard-of-care treatment is administered, in order to minimize the variability in care and filter out those patients with significant wound healing simply due to improved compliance with standard-of-care treatment (FDA guidance, page 8).
- Baseline wound characteristics can also impact the assessment of the outcome. Wounds differ in pathophysiology; therefore "it is difficult to generalize results obtained from a trial conducted in subjects with one wound type to patients with another wound type" (FDA guidance, page 2). The guidance addresses the issues surrounding proper wound assessment and quantification (FDA guidance, pages 6-7).
- Blinding of patients and investigators is advisable when feasible in order to reduce the chance for bias. If it is impractical or unethical to do so, at least a blinded assessment by a third-party evaluator should be incorporated into the trial design (FDA guidance, page 5).
- The FDA guidance states that there are generally two broad categories of endpoints to demonstrate the efficacy of wound treatment products for regulatory approval: improved wound healing and improved wound care. Examples of specific endpoints to demonstrate improved wound healing include incidence of complete wound closure, accelerated wound closure, facilitation of surgical wound closure, and quality of healing (cosmesis and function). Examples of specific endpoints to show improved wound care include treatment of wound infection, debridement, and wound pain control (FDA guidance, pages 12-15).

CMS recognizes that products such as graftskin and becaplermin were required to conduct controlled clinical trials in order to obtain FDA approval or marketing clearance for the indication of improved wound healing. This is in contrast to the reduced regulatory barrier for the indication of wound management.

B. Discussion of evidence reviewed

1. Questions:

The development of an assessment in support of Medicare coverage decisions is based on the same general question for almost all requests: "Is the evidence sufficient to conclude that the application of the technology under study will improve health outcomes for Medicare patients?" For this NCD, the questions of interest are:

- Is the evidence sufficient to conclude that the use of autologous PRP for chronic, non-healing wounds, compared to usual wound care, significantly and reliably improves the rate of complete healing in the Medicare population?
- Is the evidence sufficient to conclude that the use of autologous PRP for acute surgical wounds, compared to usual wound care, significantly and reliably improves the rate of complete healing in the Medicare population when PRP is applied directly to the closed incision?
- Is the evidence sufficient to conclude that the use of autologous PRP for dehiscent wounds, compared to usual wound care, significantly and reliably improves the rate of complete healing in the Medicare population?

2. External technology assessments

On October 30, 2007, the Cochrane database, the NICE database, the Blue Cross/Blue Shield TEC database, and the Canadian Agency for Drugs and Technologies in Health database were searched using the terms "wound care," "platelet gel," and "platelet-rich plasma." No technology assessments were found.

AHRQ released a technology assessment dated March 8, 2005 titled "Usual Care in the Management of Chronic Wounds: A Review of the Recent Literature." This technology assessment presented a broad review of the products, techniques, and protocols used in wound management and did not address autologous PRP specifically except to state that growth factors "show promise but need further, more rigorous evaluation."

3. Internal technology assessments

On September 13, 2007, CMS performed a PubMed search of the literature using the following search terms in various combinations: "platelet-rich plasma," "autologous," "chronic wound," "chronic non-healing wound," "platelet gel," and "dehiscence." The limitations used were: Human, English, Trial type (Clinical Trial, Randomized Clinical Trial, Meta-analysis), Age (Adult, Middle aged, Middle-aged plus Aged, Aged, Eighty years old and older), and Date (from 2003 to the present). The date range was selected to minimally overlap the evidence reviewed in this PDM with the evidence reviewed in the 2003 decision memorandum (CAG-00190N).

The requestor and public commenters included additional sources of potential articles.

From the above article sources, CMS looked for published, peer-reviewed evidence of controlled clinical trials that provided results on the use of autologous PRP in patients with a chronic, non-healing wound, a dehiscent wound, or an acute, surgical wound where the PRP was applied directly upon the closed incision (i.e., a cutaneous application).

Using the criteria stated above, seven literature articles were identified and reviewed for chronic, non-healing wounds (two of these also studied dehiscent wounds) and two articles for acute wounds. The review of these articles is presented below and in the evidence tables are located in Appendix B.

Evidence Summary

CHRONIC WOUNDS

Barrett SL. A new approach to using growth factors in wound healing. Podiatry Today 2003;1:44-50.

Barrett presented the results from an uncontrolled, unblinded prospective study of sixteen patients (seventeen wounds) with either a diabetic, decubitis, or venous stasis ulcer or a complicated surgical wound dehiscence. Patients had to have failed at least four weeks of standard wound care, which included debridement, offloading, and topical administration of hydrocolloids; infected wounds were excluded.

Initial treatment consisted of debridement followed by autologous PRP then petrolatum-impregnated gauze and a gauze dressing. After two weeks, PRP was reapplied as needed until complete wound closure. Patients received a new topical hydrocolloid and gauze dressing daily. Autologous PRP was produced using the SmartPReP (Harvest Technologies, Corp.) system. The primary outcome investigated was complete wound closure.

The number of each type of wound was not stated. The number of PRP applications per patient ranged from one to five. Sixteen of seventeen wounds (94%) had complete wound closure. There was one recurrence due to non-compliance. No adverse reactions were reported. Neither the age range nor the gender ratio was provided.

The author concludes that autologous PRP is useful in the treatment of chronic wounds and that the technology is simple and effective in the office-based setting. He further predicted that widespread use will be commonplace.

Crovetti G, et al. Platelet gel for healing cutaneous chronic wounds. Transfusion and Apheresis Science 2004;30:145-151.

This was an uncontrolled, unblinded prospective study of 24 patients with either a diabetic or traumatic ulcer. Inclusion criteria were not stated but patients were excluded for the presence of infection, cellulitis, osteomyelitis, or vascular insufficiency in the wound area. The outcomes investigated were extent of wound area reduction, granulation tissue formation, wound bed cleanliness and the regression/absence of infective processes.

PRP was administered once per week preceded by saline washings and followed by the application of an occlusive dressing. Antibiotics were given as needed. The MCS+ (Haemonetics Inc.) system was used to produce PRP.

Of the 24 patients studied, only three received autologous PRP and the results of only two of these three were reported in the article. One patient was a 73 year old man with a traumatic wound who experienced a greater than fifty percent recovery after 44 applications of PRP. The other patient was a 46 year old woman with a diabetic wound who dropped out of the study after only seven PRP applications due to the onset of osteomyelitis. No adverse reactions reported.

The authors conclude that PRP use improves the treatment of cutaneous wounds. They also note that PRP application is an adjuvant treatment within a multidisciplinary treatment program for chronic, cutaneous wounds.

Mazzucco L, et al. The use of autologous platelet gel to treat difficult-to-heal wounds: a pilot study. Transfusion 2004;44:1013-1018.

In Mazzucco, 2004, the authors presented the results of a nonrandomized, unblinded, prospective study that used a retrospective control group. The inclusion and exclusion criteria were not stated. There were 53 patients with either a dehiscent sternal wound or a necrotic skin ulcer. The necrotic skin ulcer resulted from various underlying causes including venous insufficiency, arterial insufficiency, trauma, or pressure. The article separately presented the treatment protocol and results for each group.

Dehiscent Sternal Wounds

In the treatment group, autologous PRP was administered twice per week. The control group received daily washing and cleaning with ialuronic acid; one patient received hyperbaric therapy. Antibiotics were given as needed. The specific system used to produce the PRP was not stated. The outcomes were time to complete healing and total hospital length of stay.

Ten patients received PRP and twelve received control therapy. The mean age was 64 years in the PRP group and 66 years in the control group. There were six men in the PRP group andeight men in the control group.

The median time to complete healing in the PRP group compared to the control group was 3.5 weeks versus 6 weeks ($p= 0.0002$). The median total hospital length of stay in the PRP group compared to the control group was 31.5 days versus 52.5 days ($p< 0.0001$). Data from the patient who received hyperbaric therapy were censored during statistical analysis.

No adverse reactions were reported.

Necrotic Skin Ulcers

In the treatment group, saline washings were followed by autologous PRP once per week. The control group received daily washing and cleaning with ialuronic acid;one control patient also received autologous cultured fibroblasts. Antibiotics were given as needed. The specific system used to produce the PRP was not stated. The outcome was the time to the necessity for surgery.

Seventeen patients received PRP and fourteen received control therapy. The mean age was 61 years in the PRP group and 63 years in the control group. There wereeight men in the PRP group andfive men in the control group.

The median time to the necessity for surgery in the PRP group compared to the control group was 15 weeks versus 35.5 weeks ($p < 0.0001$). Data from the patient who received autologous cultured fibroblasts were censored during statistical analysis.

No adverse reactions were reported.

The authors conclude that autologous PRP is easy to prepare, accessible to most physicians in metropolitan areas and areas with hospital facilities, and clinically effective. It should be used in conjunction "with the other typical treatments known to quicken tissue repair and regeneration."

McAleer JP, et al. Use of autologous platelet concentrate in a nonhealing lower extremity wound. Advances in Skin and Wound Care 2006;September:354-362.

McAleer, et al. presented a single case report of a 57 year old man with a diabetic wound who had complete closure of his wound after debridement and weekly autologous PRP followed by a compressive dressing. A Biomet Orthopedics Inc. system was used to produce the PRP. No adverse reactions were reported.

The authors conclude that autologous PRP shows "tremendous potential, warrants consideration in the treatment of recalcitrant wounds, and merits additional investigation."

Klayman MH, et al. Autologous platelet concentrate and vacuum-assisted closure device use in a nonhealing total knee replacement. Journal of Extra-Corporeal Technology 2006;38:44-47.

This article presented a single case report about a 51 year old man with diabetes who had a chronic non-healing incisional wound after total knee arthroplasty. Autologous PRP was administered about once per week for four weeks. A continuous vacuum-assisted wound closure device was applied after each PRP treatment. The SmartPReP (Harvest Technologies, Corp.) system was utilized to produce the PRP.

The wound size decreased from 15x15 cm to 8x6 cm with sufficient granulation tissue to proceed to skin grafting.

No adverse reactions were reported.

The authors conclude that with or without a vacuum-assisted closure device, autologous PRP "may prove valuable as an adjunct to good wound care and may shorten the amount of time to healing."

McAleer JP, Kaplan E, Persich G. Efficacy of concentrated autologous platelet-derived growth factors in chronic lower-extremity wounds. Journal of the American Podiatric Medical Association 2006;96(6):482-488.

This was an uncontrolled, unblinded prospective study of 24 patients with a chronic non-healing lower extremity ulcer treated unsuccessfully for at least six months with traditional methods. Patients with ankle-arm indices of less than 0.60, signs of systemic or lower extremity soft tissue infection, radiographic evidence of osteomyelitis or gangrenous changes were excluded. The wound types studied were due to venous stasis, pressure, arterial insufficiency, trauma, or diabetes-induced neuropathic pathology.

Initial treatment consisted of debridement, autologous PRP, sterile gauze and a compressive dressing. Debridement and PRP administration occurred every two weeks until the wound was completely closed. A Biomet Orthopedics Inc. system was used to produce the PRP. The patient was also instructed to limit weight-bearing activities. The outcome studied was complete wound closure.

The 24 patients had a total of 33 wounds. There were three venous stasis ulcers, two decubitis ulcers, five ulcers due to arterial insufficiency, eight traumatic ulcers in patients with diabetes, and six ulcers due to diabetes-induced neuropathic pathology. The age range was 25 to 91 years. There were thirteen women and eleven men.

Six patients did not complete the study; two patients were lost to follow-up, two patients discontinued due to the need for below-the-knee amputation due to infection, one patient had skin grafting, and one patient had wound closure during surgical correction of an anatomic deformity. Twenty of the 33 wounds (61%) had complete wound closure. The mean time to complete closure was eleven weeks. Five of the 33 wounds had no improvement.

No adverse reactions were reported.

The authors conclude that their results show that the use of autologous PRP "facilitates the reduction and closure of chronic lower-extremity wounds" in various wound types.

Driver VR, et al. A prospective, randomized, controlled trial of autologous platelet-rich plasma gel for the treatment of diabetic foot ulcers. Ostomy/Wound Management 2006;52(6):68-87.

Driver, et al. conducted a prospective, randomized, double-blinded, controlled, multi-center clinical trial in patients with a diabetic foot ulcer. Patients had to be between eighteen and 95 years old and have adequate arterial perfusion. The wound area had to be between 0.5 and twenty square centimeters (inclusive), be full-thickness without exposure of tendon, muscle, ligaments or bone, and have a distance of at least four centimeters from other wounds. Patients were excluded if the wound was infected or the hemoglobin A1C was twelve or greater.

There was a seven-day screening period, which included a baseline wound assessment and debridement, and the application of control saline gel. The patient was excluded from the trial if a greater than fifty percent reduction in wound size occurred during this screening period.

A twelve-week treatment period was followed by a twelve-week follow-up period. The PRP group received debridement, autologous PRP, a contact layer dressing, and then foam dressing. The Autologel (Cytomedix Inc.) system was used to produce the PRP. The control group received debridement, normal saline gel, a contact layer dressing, and then foam dressing. Treatment was applied twice per week until the wound completely healed, the twelve-week treatment phase ended, or the patient withdrew or was withdrawn from the study. All patients used fixed ankle-foot orthoses, and crutches or a walker.

During the twelve-week treatment phase, treatment was restarted if a completely closed wound re-opened.

The primary outcome was incidence of complete wound closure. The secondary outcomes consisted of the percent change in wound area from baseline, the percent change in wound volume from baseline, the area closure rate/day, and the volume closure rate/day. A number of efficacy analyses were performed as presented below.

Intent-To-Treat Efficacy Analysis

The clinical protocol first called for a primary efficacy analysis based on the biostatistical principle of intention-to-treat.

For this analysis, the sample size was 72 with 40 patients in the PRP group and 32 in the control group. The mean age was 56 years in the PRP group and 57 years in the control group. Eighty percent of the patients were men in the PRP group and 84% were men in the control group. The mean wound area was four square centimeters (standard deviation of five) for the PRP group and three square centimeters (standard deviation of three) for the control group. The mean wound volume was 1.7 cubic centimeters (standard deviation of four) for the PRP group and 0.9 cubic centimeters (standard deviation of 1.2) for the control group. The wide variability in baseline wound volume was statistically significantly greater in the PRP group compared to the control group ($p<0.0001$). There were no other statistically significant baseline differences between groups.

For the primary outcome, thirteen of forty patients (32.5%) in the PRP group and nine of 32 patients (28%) in the control group had complete wound closure ($p=0.79$). The results of the efficacy analysis of the secondary outcomes were not reported.

A subsequent independent audit of the study showed a 44% rate of protocol violations (32/72) that prompted a revision of the sample size and a second efficacy analysis of the primary outcome. This second analysis was called "per protocol" and the results are presented below.

Also of note, the amount of inter-site enrollment variability prompted the investigators to group the sites during the first round of statistical analysis. Five groups were formed and labeled as teaching facilities, army facility, physicians in private practice (two distinct sites) or ambulatory care clinics. One of these five groups was eliminated during the audit. For the remaining four investigational site groups, a wide variation in healing outcomes was found—fifty to one hundred percent variability in the PRP group and 25-67% variability in the control group.

Per Protocol Efficacy Analysis

The revised sample size was forty, with nineteen patients in the PRP group and 21 in the control group. There were no statistically significant differences between groups at baseline except the percent of Caucasians in the PRP group was greater than in the control group ($p=0.02$).

For the efficacy analysis of the primary outcome, thirteen of nineteen patients (68%) in the PRP group and nine of 21 patients (43%) in the control group had complete wound closure ($p=0.125$). The results of the per protocol efficacy analysis of the secondary outcomes were not reported. However, an efficacy outcome called the Kaplan-Meier median time to complete closure was reported. The median time was 45 days in the PRP group and 85 days in the control group ($p=0.126$).

The authors note that an examination of the size frequency distributions revealed that 35 of forty (88%) wounds had an area of seven square centimeters or less and a volume of two cubic centimeters or less. This subset sample of the database was called the majority wounds group and was the subject of another efficacy analysis. The results of this analysis are presented below.

Subset Efficacy Analysis

The new sample size was 35 with sixteen patients in the PRP group and nineteen in the control group.

For the efficacy analysis of the primary outcome, thirteen of sixteen patients (81%) in the PRP group and eight of nineteen patients (42%) in the control group had complete wound closure (p=0.036). The results of the subset efficacy analysis of the secondary outcomes were not reported.

No statistically significant differences in the rate of adverse events were seen between PRP and control groups (total n=72).

The authors conclude that autologous PRP use "may not only enhance healing, but it also may prevent lower extremity amputations caused by nonhealing wounds." They also note that a future study that incorporates a larger sample size can be done to validate the results from their trial.

ACUTE WOUNDS

Trowbridge CC, et al. Use of Platelet gel and its effects on infection in cardiac surgery. Journal of Extra-Corporeal Technology 2005;37:381-386.

This was a prospective, nonrandomized, unblinded, single center study of patients greater than nineteen years old who were undergoing cardiac surgery from October, 2002 to June, 2005. Sternal incision site, and vein and artery harvest site incisions were investigated. No exclusions were stated. There were three groups studied: the PRP group, the concurrent control group and the historical control group (surgical patients from the eighteen months prior to the start of the study).

Autologous PRP was applied first to the subcutaneous area of the incisional sites and then directly on the cutaneous incision after closure. For the control groups, the incisional sites received standard intra-operative and post-operative care. About fifteen percent of patients in the PRP group received PRP produced using a COBE Cardiovascular Inc. system; about seventy percent of patients received PRP produced using the CATS (Terumo Cardiovascular Systems Corp.) system; and about fifteen percent of patients received PRP produced using the SmartPReP (Cytomedix Inc.) system.

The outcome assessed was the rate of superficial and deep sternal wound infections. Subgroup data analysis was planned to determine the risk factors for infection.

The total sample size was 2,259 with 382 in the PRP group, 948 in the concurrent control group and 929 in the historical control group. The mean age was 64 years for the PRP group, 64 years for the concurrent control group and 65 years for the historical control group. The percentage of men in each group was 66% (PRP group), 65% (concurrent control group) and 64% (historical control group).

The rate of infection of superficial wounds was 0.3% in the PRP group, 1.8% in concurrent control group, and 1.5% in the historical control group ($p < 0.05$ for the PRP group compared to each control group).

The rate of infection of deep sternal wounds was 0% in the PRP group, 1.5% in concurrent control group, and 1.7% in the historical control group ($p < 0.01$ for the PRP group compared to each control group).

The low rate of infection overall precluded a subgroup analysis to determine the risk factors for infection.

The authors conclude that their results suggest the continued use of autologous PRP in patients with acute sternal wounds; however, its use "requires further prospective analysis to ascertain its benefit for improving outcomes." They also note that future studies should employ large sample sizes and measures of product quality. Lastly, consensus is needed regarding a uniform measure of infection and wound dehiscence, measures of product quality, and reporting of adverse events.

Hom DC, Linzie BM, Huang TC. The healing effects of autologous platelet gel on acute human skin wounds. Archives of Facial Plastic Surgery 2007;9:174-183.

Hom, et al. conducted a prospective, controlled, pilot study in healthy adult volunteers. Volunteers were excluded if there was a history of diabetes, keloid/scar formation, collagen vascular disease or bleeding disorder, or use of an anticoagulant or steroid during the month prior to enrollment.

Each volunteer received five full-thickness, punch biopsy wounds of four to six millimeters in diameter on each thigh. A punch wound and its corresponding punch wound on the other thigh were considered a "set." There were eight volunteers for a total of 80 wounds.

For each volunteer, each of the five sets of thigh punch wounds was assigned to one of five groups and one of two phases:

Phase 1

Group	PRP	Control
1	Applied on Day 0 + petrolatum ointment	Topical antibiotic
2	Applied on Day 0	None

Phase 2

Group	PRP	Control
3	Applied on Days 0 & 7 + petrolatum ointment	Topical antibiotic
4	Applied on Days 0 & 7	None

Group 5 punch wounds were allowed to heal by secondary intention alone.

All wounds were covered with a semi-occlusive dressing.

The Magellan (Medtronic Inc.) system was used to produce autologous PRP.

Wound healing measurements were recorded for 42 days. Clinical assessment and blinded photographic assessment was used to study the percent wound closure over time, and the time required for complete wound closure.

The age range studied was 21 to 58 years and four of the eight volunteers were men.

The results appear to be pooled across groups one through four for autologous PRP-treated and for control-treated groups, and then reported as PRP-treated versus control, despite the fact that each set of PRP-treated punch wounds received slightly different treatment. The text of the article gives an incomplete presentation of the percent wound closure over time results. Based on clinical assessment, for day 7 the mean (SE) percent wound closure over time was 14% (1.1) for the PRP wounds and 7% (1.1) for the control wounds. For day 14, the mean (SE) percent wound closure over time was 73.9% (2.9) for the PRP wounds and 49.6% (3.6) for the control wounds. For day 17, the mean (SE) percent wound closure over time was 81.1% (2.5) for the PRP wounds and 57.2% (5.9) for the control wounds. The article text does not provide the results out to day 42 but a chart does provide this information.

In the chart, there is dispersion in the data between the PRP-treated and control groups from day 7 through to day 31, with the PRP-treated group showing a greater mean percent closure compared to the control group. The widest dispersion between the groups occurs at days 14 and 17. By day 35 both groups show 100% closure. The chart does not indicate the degree of variation around each data point. The presence or absence of statistical significance at each data point is also not indicated on the graph; however, in the text accompanying the chart the authors state "autologous platelet gel (APG)-treated sites had increased wound closure compared with the control sites over a 42-day period (P<.001)." Based on the data from digital photography, the authors state "the APG-treated sites had significantly increased wound closure compared to control sites over a 42-day period (P=.02, analysis of variance with repeated measures)."

For the outcome of time required for complete wound closure, on day 21, 63% of the PRP-treated wounds and 31% of the control wounds had complete closure. On day 24, 81% of the PRP-treated wounds and 44% of control wounds had complete closure. On day 28, 88% of the PRP-treated wounds and 56% of control wounds had complete closure. The average time to achieve complete closure was 29.75 days for the PRP-treated wounds and 35.38 days for the control wounds. None of these results achieved statistical significance.

No infections or serious adverse events were reported.

The authors conclude their results need to be confirmed by future studies. If its effectiveness is confirmed, autologous PRP use "could have a useful impact on the enhancement of postoperative dermal wound healing in surgical patients."

4. MedCAC

No MedCAC was convened for this topic.

5. Evidence-based guidelines

A summary clinical algorithm for a guideline by the Association for the Advancement of Wound Care was found during a search of the National Guideline Clearinghouse database. The algorithm, titled "Summary algorithm for venous ulcer care with annotations of available evidence" briefly notes the use of biologic dressings for wounds at least 30 days old as well as the use of platelet-derived growth factor. However, an evidence strength rating of "C" was assigned to each. This rating means that at least one of the following is lacking: results from a controlled trial, results of at least 2 case series or descriptive studies or a cohort study in humans, or expert opinion.

In 2006, the Wound Healing Society published evidence-based guidelines to demonstrate the best care of chronic wounds. The guidelines were presented by type of chronic wound (diabetic ulcers, venous ulcers, pressure ulcers, and arterial insufficiency ulcers). Only the venous ulcer guideline addressed a PRP-type of treatment and noted that this treatment has "yet to be shown to demonstrate sufficient statistically significant results or effectiveness to recommend" its use.

6. Professional Society Position Statements

An internet search failed to locate any professional society position statements exclusively concerning autologous PRP.

7. Public Comments

During the initial 30-day public comment period, CMS received a total of61 comments. Of the comments, fifty-seven were in favor of coverage, three opposed coverage, and one expressed no clear indication for coverage. Comments that were submitted via CMS coverage website may be viewed by using the following link: http://www.cms.hhs.gov/mcd/viewpubliccomments.asp?nca_id=208

A. Comments with evidence

CMS received a total of eleven comments that referred to evidence. Two of these comments were non-supportive of coverage; the remaining comments were supportive. Articles and information provided as evidence included studies and information already mentioned; studies of PRP used in a manner unrelated to this PDM; unpublished studies; studies published in abstract form only; basic/bench research or animal studies; review articles; studies of non-PRP products; and cited references that could not be found using PubMed.

Basic research studies and animal studies generally do not provide evidence of clinical benefit that is particularly pertinent to CMS. Review articles do not provide additional information. Unpublished, and therefore, non-peer-reviewed, information generally is accorded less weight than published and peer-reviewed material. Studies of the non-cutaneous use of PRP are not relevant to the cutaneous benefit of PRP.

Supporters
Many commenters in this category cited that use of autologous PRP reduces risk of limb amputations in diabetic patients. One commenter stated that autologous PRP has become a standard treatment in sternal wound healing of cardiac patients. Another commenter added that this treatment has been "extensively utilized as the prevalent blood product for treating chronic non-healing wounds, open cutaneous wounds, soft tissue, and bone." This commenter continues on to say that the benefits of this treatment have been demonstrated through many studies including those with clinically significant outcomes.

Non-supporters
One commenter stated that CMS should deny Cytomedix's request for Medicare coverage because the use of platelet rich plasma has not been cleared or approved by the U.S. Food and Drug Administration and "there is no clinical data demonstrating the safety and efficacy of PRP gel for treating these chronic cutaneous ulcers."

Another commenter restricted comments to address the coverage of PRP for wounds caused by acute surgical incisions or dehiscence. This commenter suggests that CMS should insist on requesting long-range randomized clinical trials with a large number of enrollees involving several institutions. This concludes that the current research does not meet those standards.

B. Comments without evidence

CMS received 50 comments without evidence. Only one commenter in this category opposed coverage and one commenter did not express a clear preference regarding coverage.

Physicians/Surgeons
Of this category, CMS received comments from eleven physicians and surgeons. One commenter suggested that the use of PRP has been shown to speed granulation tissue formation in many patients with exposed bone and/or tendon which has allowed progression to a healed wound. One commenter stated that blood derived products work as well as other therapies covered by CMS.

Perfusionists
CMS received nine comments from perfusionists that did not include evidence. One commenter stated that all wound care centers report that platelet gel improves wound healing much better than conventional wound therapy. Another commenter claimed that there are many advantages to using platelet gel for most wound healing cases and surgical procedures.

Other Healthcare Professionals
CMS received twenty-one comments without evidence from other healthcare professionals. This category contains individuals within healthcare industry, such as: nurses, professors, professional societies, manufactures, etc.

One commenter stated that in chronic wounds the physical environment is superseded by underlying physiological processes and to significantly improve chronic wound healing one must go further to address biological mechanisms that undermine the ability to heal. This commenter strongly recommended the use of autologous PRP to address this issue. Another commenter said, "I know that PRP treatment is not going to be the primary method for wound closure, however when patients do not respond to traditional therapy, they need options to give them hope and a chance at full recovery."

The one commenter who was against coverage suggests that more research is needed in the claim that growth factors promote wound healing. Another commenter expressed no indication for coverage but expressed this procedure should be monitored closely.

Patients/General Public

CMS received comments from eight patients and one from the general public. Many commenters explained how the use of autologous PRP improved their wound healing and lessened pain after surgery. Other commenters suggested that the use of platelet gel improved healing time of their ulcers. The commenter from the general public commented on an acquaintance who used this treatment with positive results. Most commenters in this group mentioned that this product improves quality of life and saves Medicare money.

VIII. CMS Analysis

National coverage determinations (NCDs) are determinations by the Secretary with respect to whether or not a particular item or service is covered nationally under title XVIII of the Social Security Act § 1869(f)(1)(B). In order to be covered by Medicare, an item or service must fall within one or more benefit categories contained within Part A or Part B, and must not be otherwise excluded from coverage. Moreover, with limited exceptions, the expenses incurred for items or services must be "reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member." § 1862(a)(1)(A).

CMS focused on three general questions as noted in the introduction to the evidence section. The analysis of the evidence will be presented by question.

Chronic, non-healing wounds

Is the evidence sufficient to conclude that the use of autologous PRP for chronic, non-healing wounds, compared to usual wound care, significantly and reliably improves the rate of complete healing in the Medicare population?

The evidence base for chronic, non-healing wounds consisted of the results from seven articles. Two of these articles presented a controlled study; one was prospectively controlled, randomized, and double-blinded (Driver, 2006) while the other one was retrospectively controlled (Mazzucco, 2004). The remaining articles presented an uncontrolled study; either as a series of cases (Barrett, 2003; Crovetti, 2004; McAleer, 2006) or as a single case report (McAleer, 2006; Klayman, 2006).

The lack of randomization and blinding in uncontrolled study designs such as case reports and case series significantly impairs the ability to come to confident conclusions. Evidence generated from such study designs can suggest that a treatment may be useful but a controlled study design is needed to confirm a beneficial health outcome. Hence, the evidence found in Barrett, 2003; Crovetti, 2004; McAleer, 2006; McAleer, 2006; and Klayman, 2006 is interesting but not very useful for determining the health benefit of autologous PRP in patients with chronic, non-healing wounds.

The retrospectively controlled study employed by Mazzucco, et al. is an improvement over the uncontrolled study designs because it incorporates a comparator and permits a statistical analysis to determine if a statistically (as well as a clinically) significant difference in health outcome is achieved with the use of a particular treatment. However, this control group created from past health records has some potential sources of bias including a lack of randomization and blinding as well as the possibility that an outdated type of care was provided or the standard of care was provided in an inconsistent manner. These potential pitfalls must be taken into consideration when interpreting the results from Mazzucco, et al.

A prospectively controlled study design allows for the use of randomization and blinding, which can lead to the generation of robust evidence by limiting bias and confounding. This type of study design is noted prominently in the FDA guidance as presented in the introduction to the Evidence section of this proposed decision memorandum. Of the seven articles investigating the use of autologous PRP in patients with a chronic, non-healing wound, only the article by Driver, et al. used a prospectively controlled study design. Unfortunately, this study suffered from significant deficiencies during the conduct of the protocol that negatively impacted the data quality and statistical analysis. Consequently, a statistically significant result was not found until the authors narrowed down the evidence database and performed a previously unplanned statistical analysis. Hence, the results of this study can serve to generate hypotheses for future randomized, controlled trials but not to conclusively demonstrate the ability of autologous PRP to improve the rate of wound closure in patients with chronic, non-healing wounds.

Taken together, the seven articles had a total sample size of 169 patients. Fifty-eight of these patients received various control therapies and 111 patients were given autologous PRP. The majority of these patients (54%) had a diabetic ulcer and the next largest group of patients had a sternal dehiscent wound (15%). These figures are only estimates, however, since one of the seven articles did not break out the sample size by wound type. Regardless, this is a very small number of patients investigated, especially given the variety of wound types that were studied. The differing pathophysiology and potential differing response to treatment of each type of wound could have negatively impacted the chance of this evidence to demonstrate a positive health outcome of autologous PRP in patients with chronic, non-healing wounds.

Another potential limiting factor on the ability of this evidence to demonstrate a positive health outcome in this patient population is the quality of PRP. The production of PRP involves a number of steps and ingredients at the "point-of-care." While a procedure is typically defined upfront, the consistency of application from patient to patient can be impacted by a number of factors including patient factors (e.g., blood platelet count), ingredient factors (e.g., thrombin quality; source of blood), and process factors (e.g., the type of centrifuge used, centrifugation time and RPMs; method of growth factor release). In his review of PRP from 2004, Marx notes that "not all currently marketed PRP devices are equal" and that studies "suggesting that there is no benefit from PRP can often be traced to poor-quality PRP produced by inadequate devices." CMS sought to minimize the impact of PRP quality by focusing only on autologous rather than homologous PRP; however, it was not possible to control for most of the potential limiting factors.

In the 2003 decision memorandum (CAG-00190N), CMS issued a national non-coverage determination for autologous PRP (except when used for chronic wounds in accordance with the clinical trial policy) based upon the absence of evidence of health benefits of the use of the treatment in this population. In the current PDM, suggestive evidence is now available for review; however this evidence is significantly limited in quality and therefore inadequate.

Acute wounds

Is the evidence sufficient to conclude that the use of autologous PRP for acute surgical wounds, compared to usual wound care, significantly and reliably improves the rate of complete healing in the Medicare population when PRP is applied directly to the closed incision?

Two articles (Trowbridge, 2005; Hom, 2007) were reviewed to assess the use of autologous PRP in an acute wound. Trowbridge, et al. performed a prospective study in patients undergoing cardiac surgery that compared autologous PRP to a concurrent control group and a retrospective control group. The sample size was large; however, the study design suffered from a lack of randomization and blinding. Three different systems were used to produce the autologous PRP, which introduced a potential source of variability in the outcomes data. Despite these possible limitations, a statistically significant improvement was reported in the rate of superficial and in the rate of deep sternal wounds in the autologous PRP group compared to each control group.

Hom, et al. investigated the percent wound closure over time and the time required for complete wound closure, compared to a control, in healthy volunteers. This study was not randomized and the clinical assessor was not blinded. However, the assessor of the wound photographs was blinded. The authors reported statistically significantly increased wound closure in the PRP group compared to the control group. While the quantity of information reported in the article was large, the quality of the reported information was poor. It was difficult to precisely determine the study methodology. Reporting of the results was confusing. All of the data from the four autologous PRP-treated groups appeared to be pooled although each group received slightly different treatment. The same was true for the four control groups. These deficiencies impair the ability to draw confident conclusions from the evidence.

The evidence reviewed from one study suggests that autologous PRP provides a benefit to patients with acute surgical wounds. The second study also suggests that autologous PRP is beneficial but was limited to healthy people who were less than 65 years of age and therefore is not representative of the Medicare population.

Overall, the evidence reviewed regarding the use of autologous PRP in patients with acute surgical wounds is limited in quantity and quality. The evidence is not adequate to demonstrate that autologous PRP is reasonable and necessary, compared to usual wound care. Consequently, autologous PRP is not reasonable and necessary for use in acute surgical wounds in the Medicare population when PRP is applied directly to the closed incision.

Dehiscent wounds

Is the evidence sufficient to conclude that the use of autologous PRP for dehiscent wounds, compared to usual wound care, significantly and reliably improves the rate of complete healing in the Medicare population?

Two articles presented evidence concerning the use of autologous PRP in patients with a dehiscent wound (Barrett, 2003; Mazzucco, 2004). Barrett, et al. did not present the results by wound type; therefore, it is not possible to determine an outcome for just patients with dehiscent wounds.

Mazzucco, et al. did separately report the results for patients with dehiscent wounds. A statistically significant improvement in the median time to complete healing and in the median total hospital length of stay was seen in the autologous PRP group compared to a retrospective control group. As noted in the analysis for patients with chronic, non-healing wounds, this evidence suffers from a small sample size, and the lack of a study design that includes randomization and blinding in order to minimize bias and confounding.

The evidence reviewed suggests that autologous PRP provides a benefit to patients with dehiscent wounds; however, due to limitations in quantity and quality, the evidence is not adequate to demonstrate that autologous PRP is reasonable and necessary, compared to usual wound care. Consequently, autologous PRP is not reasonable and necessary for use in dehiscent wounds in the Medicare population.

Conclusions

The evidence is not adequate to conclude that the use of autologous PRP for chronic, non-healing wounds, compared to usual wound care, significantly and reliably improves the rate of complete healing in the Medicare population.

The evidence is not adequate to conclude that the use of autologous PRP for acute surgical wounds, compared to usual wound care, significantly and reliably improves the rate of complete healing in the Medicare population when PRP is applied directly to the closed incision.

The evidence is not adequate to conclude that the use of autologous PRP for dehiscent wounds, compared to usual wound care, significantly and reliably improves the rate of complete healing in the Medicare population.

IX. Proposed Decision

The Centers for Medicare and Medicaid Services (CMS) proposes the following:

The evidence is not adequate to determine that autologous platelet rich plasma (PRP) is reasonable and necessary for the treatment of chronic non-healing cutaneous wounds, acute surgical wounds when the autologous PRP is applied directly to the closed incision, or dehiscent wounds. CMS is proposing to issue non-coverage determinations for acute surgical wounds when the autologous PRP is applied directly to the closed incision and for dehiscent wounds.

In addition, we propose to make no change to the NCD addressing Blood-Derived Products for Chronic Non-Healing Wounds (Pub. 100-3, 270.3.D). In accordance with section 310.1 of the National Coverage Determinations Manual, Medicare covers the routine costs in Federally sponsored or approved clinical trials assessing the efficacy of autologous PRP in treating chronic, non-healing cutaneous wounds.

We are requesting public comments on this proposed determination pursuant to Section 1862(l) of the Social Security Act. We are particularly interested in comments that include new evidence we have not reviewed here. After considering the public comments and any additional evidence, we will make a final determination and issue a final decision memorandum.

Appendix A: General Methodological Principles of Study Design

When making national coverage determinations, CMS evaluates relevant clinical evidence to determine whether or not the evidence is of sufficient quality to support a finding that an item or service falling within a benefit category is reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member. The critical appraisal of the evidence enables us to determine whether: 1) the specific assessment questions can be answered conclusively; and 2) the intervention will improve health outcomes for patients. An improved health outcome is one of several considerations in determining whether an item or service is reasonable and necessary.

CMS normally divides the assessment of clinical evidence into three stages: 1) the quality of the individual studies; 2) the relevance of findings from individual studies to the Medicare population; and 3) overarching conclusions that can be drawn from the body of the evidence on the direction and magnitude of the intervention's risks and benefits.

The issues presented here represent a broad discussion of the issues we consider when reviewing clinical evidence. However, it should be noted that each coverage determination has unique methodological aspects.

1. Assessing Individual Studies

Methodologists have developed criteria to determine weaknesses and strengths of clinical research. Strength of evidence generally refers to: 1) the scientific validity underlying study findings regarding causal relationships between health care interventions and health outcomes; and 2) the reduction of bias. In general, some of the methodological attributes associated with stronger evidence include those listed below:

- Use of randomization (allocation of patients to either intervention or control group) in order to minimize bias.
- Use of contemporaneous control groups (rather than historical controls) in order to ensure comparability between the intervention and control groups.
- Prospective (rather than retrospective) studies to ensure a more thorough and systematical assessment of factors related to outcomes.
- Larger sample sizes in studies to help ensure adequate numbers of patients are enrolled to demonstrate both statistically significant as well as clinically significant outcomes that can be extrapolated to the Medicare population. Sample size should be large enough to make chance an unlikely explanation for what was found.

- Masking (blinding) to ensure patients and investigators do not know to which group patients were assigned (intervention or control). This is important especially in subjective outcomes, such as pain or quality of life, where enthusiasm and psychological factors may lead to an improved perceived outcome by either the patient or assessor.

Regardless of whether the design of a study is a randomized controlled trial, a non-randomized controlled trial, a cohort study or a case-control study, the primary criterion for methodological strength or quality is the extent to which differences between intervention and control groups can be attributed to the intervention studied. This is known as internal validity. Various types of bias can undermine internal validity. These include:

- Different characteristics between patients participating and those theoretically eligible for study but not participating (selection bias)
- Co-interventions or provision of care apart from the intervention under evaluation (confounding)
- Differential assessment of outcome (detection bias)
- Occurrence and reporting of patients who do not complete the study (attrition bias)

In principle, rankings of research design have been based on the ability of each study design category to minimize these biases. A randomized controlled trial minimizes systematic bias (in theory) by selecting a sample of participants from a particular population and allocating them randomly to the intervention and control groups. Thus, randomized controlled studies have been typically assigned the greatest strength, followed by non-randomized clinical trials and controlled observational studies. The following is a representative list of study designs (some of which have alternative names) ranked from most to least methodologically rigorous in their potential ability to minimize systematic bias:

- Randomized controlled trials
- Non-randomized controlled trials
- Prospective cohort studies
- Retrospective case control studies
- Cross-sectional studies
- Surveillance studies (e.g., using registries or surveys)
- Consecutive case series
- Single case reports

When there are merely associations but not causal relationships between a study's variables and outcomes, it is important not to draw causal inferences. Confounding refers to independent variables that systematically vary with the causal variable. This distorts measurement of the outcome of interest because its effect size is mixed with the effects of other extraneous factors. For observational, and in some cases randomized controlled trials, the method in which confounding factors are handled (either through stratification or appropriate statistical modeling) are of particular concern. For example, in order to interpret and generalize conclusions to our population of Medicare patients, it may be necessary for studies to match or stratify their intervention and control groups by patient age or co-morbidities.

Methodological strength is, therefore, a multidimensional concept that relates to the design, implementation and analysis of a clinical study. In addition, thorough documentation of the conduct of the research, particularly study's selection criteria, rate of attrition and process for data collection, is essential for CMS to adequately assess the evidence.

2. Generalizability of Clinical Evidence to the Medicare Population

The applicability of the results of a study to other populations, settings, treatment regimens, and outcomes assessed is known as external validity. Even well-designed and well-conducted trials may not supply the evidence needed if the results of a study are not applicable to the Medicare population. Evidence that provides accurate information about a population or setting not well represented in the Medicare program would be considered but would suffer from limited generalizability.

The extent to which the results of a trial are applicable to other circumstances is often a matter of judgment that depends on specific study characteristics, primarily the patient population studied (age, sex, severity of disease, and presence of co-morbidities) and the care setting (primary to tertiary level of care, as well as the experience and specialization of the care provider). Additional relevant variables are treatment regimens (dosage, timing, and route of administration), co-interventions or concomitant therapies, and type of outcome and length of follow -up.

The level of care and the experience of the providers in the study are other crucial elements in assessing a study's external validity. Trial participants in an academic medical center may receive more or different attention than is typically available in non-tertiary settings. For example, an investigator's lengthy and detailed explanations of the potential benefits of the intervention and/or the use of new equipment provided to the academic center by the study sponsor may raise doubts about the applicability of study findings to community practice.

Given the evidence available in the research literature, some degree of generalization about an intervention's potential benefits and harms is invariably required in making coverage decisions for the Medicare population. Conditions that assist us in making reasonable generalizations are biologic plausibility, similarities between the populations studied and Medicare patients (age, sex, ethnicity and clinical presentation), and similarities of the intervention studied to those that would be routinely available in community practice.

A study's selected outcomes are an important consideration in generalizing available clinical evidence to Medicare coverage determinations because one of the goals of our determination process is to assess health outcomes. We are interested in the results of changed patient management not just altered management. These outcomes include resultant risks and benefits such as increased or decreased morbidity and mortality. In order to make this determination, it is often necessary to evaluate whether the strength of the evidence is adequate to draw conclusions about the direction and magnitude of each individual outcome relevant to the intervention under study. In addition, it is important that an intervention's benefits are clinically significant and durable, rather than marginal or short-lived.

If key health outcomes have not been studied or the direction of clinical effect is inconclusive, we may also evaluate the strength and adequacy of indirect evidence linking intermediate or surrogate outcomes to our outcomes of interest.

3. Assessing the Relative Magnitude of Risks and Benefits

Generally, an intervention is not reasonable and necessary if its risks outweigh its benefits. Improved health outcomes are one of several considerations in determining whether an item or service is reasonable and necessary. For most determinations, CMS evaluates whether reported benefits translate into improved health outcomes. CMS places greater emphasis on health outcomes actually experienced by patients, such as quality of life, functional status, duration of disability, morbidity and mortality, and less emphasis on outcomes that patients do not directly experience, such as intermediate outcomes, surrogate outcomes, and laboratory or radiographic responses. The direction, magnitude, and consistency of the risks and benefits across studies are also important considerations. Based on the analysis of the strength of the evidence, CMS assesses the relative magnitude of an intervention or technology's benefits and risk of harm to Medicare beneficiaries.

Appendix B [PDF, 171KB]
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